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Environmental and Toxicological Aspects of Insect Growth Regulators

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Insect growth regulators (IGRs) are a class of new chemicals that interfere with maturation and reproduction in insects. Proposed hypotheses on the biochemical mechanism of action are presented herein. The environmental aspects as metabolism in soils, plants, insects, and animals suggest strongly that these chemicals undergo rapid degradation and metabolism to innocuous metabolites. The toxicological properties determined for registration of the IGR methoprene, isopropyl (*E,E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, reflected no significant effects against any of the species tested. Toxicological evaluations in swine, sheep, hamsters, rats, dogs, rabbits, guinea pigs, and cattle revealed no clinical signs of toxicosis. Additionally, teratological studies in swine, sheep, hamsters, rats, and rabbits also resulted in no observable effects in the animals at the levels administered.

The basic idea behind the use of juvenile hormones as pesticides is that these materials interrupt development and so cause death or reproductive failure of insects exposed at a specific time in the life cycle. It is for this reason that the term insect growth regulator (IGR) is now used to describe this class of chemicals. Initially, IGRs were primarily analogs of the cecropia juvenile hormone, (methyl *trans, trans, cis*-10-epoxy-7-ethyl-3,11-dimethyl-2,6-tridecadienoate). Subsequently, additional structures with analogous activity have been so classified.

In considering the environmental aspects of these IGRs, I should first like to consider some overt effects of the mode of action of IGRs against insects. The first is the alteration they cause in insect cuticle. Wigglesworth (*1*) recognized that a crude extract of the insect would alter the morphological structure of the adult cuticle when it was applied to immature forms of *Rhodnius* spp. We now know that insect cuticle undergoes changes that are mediated by the epidermal cells which in turn respond to endogenous hormones, and it is these morphogenetic changes that are most recognizable. Rather obviously, then, an appropriate time for the introduction of an exogenous interfering chemical is this sensitive period, just immediately prior to cell division. Indeed, Williams and Kafatos (*2*), in theorizing about the mode of action of juvenile hormones (JHs), refer to this sensitive period as the time when the JH exerts a specific influence on nucleic acid metabolism and gene activation. They therefore reflect the Jacobs-Monod theory on gene activation in microorganisms: the genome of each insect cell is divided into three main sets of genes that reflect larval, pupal, or adult differentiation. Usually, with the innate JH, the programming sequence leads to completion of metamorphosis, but if a JH is present at the wrong time, morphogenetic abnormalities occur; for example, additional molts that result in larger insects or intermediates that represent two distinct growth stages, i.e., larval-pupal or pupal-adult.

A second overt effect is the interference of IGRs with embryonic development that is reflected by nonemergence. The mechanism of action that produces this effect is unknown, though Staal (*3*) showed the activity occurs before blastokinesis. This disruption of embryogenesis has been demonstrated in Thysanura (*4*), Orthoptera (*5*), Hemiptera (*6*), Homoptera (*7*), Coleoptera (*8*), Lepidoptera (*9,10*), and Diptera (*11*). Also, in some insects (*9,12*), treatment of the egg will produce morphogenic effects in later developmental stages.

The JH is necessary in adult females for gonadotrophic activity with the most apparent

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effect being on growth and development of the ovaries (*13*). In the absence of JH, adult reproductive diapause may occur, and Bowers and Blickenstaff (*14*) first reversed this effect by applying a JH analog to diapausing alfalfa weevils, *Hypera postica* (Gyllenhal). Again, the exact mode of action is not understood. Sterilization or other changes may occur in reproduction such as reduced or increased fecundity. Morphological aberrations, i.e., the inhibition of male genital rotation in Diptera as noted by Spielman and Williams (*15*), may be produced. Masner et al. (*16–18*) reported that treated females of *Pyrrhocoris apterus* L. were sterilized, and males that mated with these subsequently transferred the sterility to untreated females during mating. However, attempts with other species have failed to produce this sterility concept with juvenile hormone analogs (JHAs).

The second approach on the mode of action of JH is that of Minks (*19*) and that of Lezzi and Frigg (*20*) who believe that phosphorylating ability is stimulated by JH which is a result of an intracellular imbalance of potassium and sodium ions. Minks showed that the intracellular Na was decreased whereas Lezzi and Frigg assumed that an increase of intracellular Na occurred after exposure to JH.

The third theory is that JH affects the membrane permeability, particularly on the internal lipoprotein membranes. Baumann (*21*) has demonstrated that certain JH will cause a depolarization of the cell membrane in salivary glands and explained this effect as an interaction with membrane lipids. Wigglesworth (*22*) has also advanced a similar hypothesis that a stereospecific membrane would be a site of action for these JH substances. Furthermore, it appears strongly that the primary effects of JH depends on the binding ability to intracellular receptor sites that may be protein or nucleoprotein molecules. This receptor specificity probably could and will be associated with genetic factors.

Another class of IGRs would be those that interfere with the formation of the insect's cuticle during molt. A representative is *N*-(4-chlorophenyl-*N'*-2,6-difluorobenzoyl)urea, (TH-6040) (*23*). Concerning its mode of action, Post and Mulder (*24*) postulated that incorporation of glucose into the endocuticle was prevented by this material. Sowa and Marks (*25*) have since demonstrated that the incorporation of ^{14}C-glucosamine into leg chitin was inhibited by TH-6040 *in vitro*. Additional roles TH-6040 plays in chitin synthesis are still under investigation (A. Verloop, Philips-Duphar B.V., personal communication).

A characteristic of TH-6040 that is not fully understood is its ability to decrease fertility in the boll weevil, *Anthonomus grandis* Boheman, when used in conjunction with the chemosterilant busulfan (1,4-butanediol dimethanesulfonate) which was fed in the boll weevil diet (*26*). Currently at my laboratory, studies with TH-6040 show that reduced fecundity and fertility can be attained with reciprocal crosses of either treated males and females with the opposite untreated sex of the stable fly and the house fly (Wright, unpublished data).

Studies on the environmental degradation of TH-6040 by Metcalf et al. (*27*) showed that it is moderately persistent in their laboratory model ecosystem in alga, snail, caterpillar, and mosquito larva. The fish, *Gambusia* spp., was able to metabolize it very efficiently which demonstrated no bioconcentration. A possible environmental concern with TH-6040 is its effect on chitin formation in nontarget arthropods as shrimp, crayfish, lobsters, and crabs.

The natural occurrence of JH substances in plants, especially in wood of coniferous species, has been shown by Slama and Williams (*28*) and by Bowers et al. (*29*). Related studies by Cerny et al. (*30*), Rogers et al. (*31*), and others have indicated that active JH compounds occurred only in some evergreens. Stowe and Hudson (*32*) reported that certain JHs acted as lipids and promoted plant growth and they suggested the point of action was at a membrane controlling respiratory function. Babu and Slama (*33*) observed that JH may cause morphogenic disturbance in insects after contact with treated plants which is suggestive of a systemic property. This is an area concerning specific biological implications that could lead to a better understanding of plant and insect interactions. Information is severely lacking on the presence and metabolism of IGRs in most plants.

Through JH bioassays, Williams et al. (*34*) found positive reactions with lipid extracts from thymus, human placenta, and various other vertebrate organs. Schneiderman and Gilbert (*35*) also reported JH activity in lipid extracts from the adrenal cortex of vertebrates, from Crustaceans, and almost all of the animal phyla, as well as in microorganisms and plants. However, the identity of the materials responsible for the JH activity was not determined. Slama et al. (*36*) reports that materials with JH activity are present in our ordinary food as milk, cream, vegetable, and plant food products.

We must keep in mind that the analogs prepared for use in insect control interfere with the normal pathways of development and may therefore not be

freely compatible with normal plant or animal biochemical functions.

Insects already have the mechanism for the metabolism of endogenous JH, probably with esterases as suggested in separate studies by Whitmore et al. (*37*) and Weirich et al. (*38*). Yu and Terriere (*39*) have demonstrated in the house fly, *Musca domestica* L., that exposure to certain insect JHAs could induce the production of detoxifying enzymes and reduce microsomal activity. Slade and Zibbitt (*40*) established that metabolism of cecropia JH occurred by ester hydrolysis. Slade and Wilkinson (*41*) also proved that the pathways for the metabolism of JH in the southern armyworm, *Spodoptera eridania* (Cramer), occurred similarly. There are many other studies on the metabolism of JH and its analogues in insects including those by Ajami and Riddiford (*42*), White (*43*), Whitmore et al. (*44,45*), Weirich and Wren (*46*). In most cases, the rate of metabolism was determined by three factors: the mode of administration, the species and developmental stage, and the site of application.

Currently, only one IGR, isopropyl (*E,E*)-11-methoxy-3, 7, 11-trimethyl-2, 4-dodecadienoate (methoprene), is registered for use. Rates of 3-4 oz A.I./acre can be applied against flood water mosquitoes, and the material has been approved as a feed additive for cattle for control of the horn fly, *Haematobia irritans* (L.).

Quistad et al. (*47*), reporting on the environmental degradation and metabolism of methoprene by alfalfa and rice, showed that it was rapidly biodegraded by both to harmless metabolites. The major metabolic pathways identified involved ester hydrolysis, *O*-demethylation, and oxidative scisson of the 4-ene double bond. Also, they noted a significant and unusual (for pesticides) conversion of the metabolites to natural products such as cellulose and possibly chlorophylls and carotenoids.

Schooley et al. (*48*) studied the metabolic fate of methoprene in soils and found that it was rapidly degraded in a variety of soils under different environmental conditions; thus persistence would not be a problem. W. F. Chamberlain of USDA (personal communication) determined the metabolic fate of methoprene in a Hereford steer and surmized that it was metabolized similar to a methyl branched fatty acid for acetate production in addition to the usual patterns of conjugative excretion. He also used a guinea pig to demonstrate the absorption, excretion, and metabolism of methoprene.

Solomon and Metcalf (*49*) reported on the metabolism and pathways of methoprene in two insects, the yellow mealworm, *Tenebrio molitor* L., and the large milkweed bug, *Oncopeltus fasciatus* (Dallas).

Another JHA that has shown promise as a selective insect control agent is R-20458, (*E*)-6,7-epoxy-1-(*p*-ethylphenoxy)-3,7-dimethyl-2-octene. The R-20458 administered intraperiotoneally (IP) to rats gave rise to polar products that appeared in urine and feces (*50*), and labeled R-20458 administered orally to rats was not detected in significant quantities in tissues or expired air (*41*). However, the metabolic transformations of R-20458 were by α and β oxidation of the 4′-ethyl moiety, by hydration of the *trans* olefin, by hydration of the 6,7-epoxy group, and by ether cleavage. Thus, R-20458 was extensively metabolized and rapidly excreted in rats.

Hammock et al. (*52,53*) determined the major metabolic pathways and products of R-20458 in the house fly, mealworm, so-called large flesh fly, *Sarcophaga bullata* Parker, tobacco hornworm, *Manduca sexta* (L.), and cabbage looper, *Trichoplusia ni* (Hubner). They reported that the relative rates and metabolism depended on the insect species, strain, and relative levels of enzymes that were involved in the inactivation pathways.

The fate of R-20458 following oral and dermal exposure to steers indicated that it was completely metabolized and quantitatively excreted after oral administration. About 85% was eliminated in the urine and about 15% in the feces. Metabolism of R-20458 by the steer was by epoxide hydration, α oxidation of the 4′-ethyl moiety, ether cleavage, and additonal underfined biotransformations. In the dermal test, about 30% of the dose was absorbed dermally and then excreted within 7 days posttreatment whereas 40% remained at the application site and 90% of this was unchanged R-20458 (*54*).

At our laboratory, several studies have been done for the evaluation of toxicological properties of this IGR. The R-20458 was given by two methods: directly or mixed into the feed. Our laboratory screening parameters included: leukocyte and erythrocyte counts; differential white count, hemoglobin, packed cell volume, platelet and reticulocyte counts; and erythrocyte fragility and also coagulation tests. Also, serum creatinine, phosphorus, urea nitrogen, uric acid, total serum proteins, protein fractions by electrophoresis, serum calcium, copper, iron, magnesium, potassium, sodium, and zinc were determined. In addition, histopathological examination was made of selected tissue sections.

Swine were given 0.5–1.0 g/kg by stomach tube or fed levels of 3000, 1000, and 300 ppm in feed daily for 13 weeks. No clinical signs of toxicity were

noted. No toxicity or teratogenic effects were observed in hamsters which received gradient doses (from 250 mg/kg through 2500 mg/kg) by intraperitoneal injection to female hamsters on day 8 of gestation. No clinical signs of toxicosis were seen in sheep that received single oral doses of 500, 750, or 1000 mg/kg body weight when given by intraruminal injection or mixed in the feed (300 or 1000 ppm) or given (50 and 100 mg/kg) in capsules daily for 13 weeks (*55,56*).

Smalley (personal communication) also tested methoprene in the drinking water of sheep for 12 weeks. He used rates of 1000, 2000, and 10,000 ppm in the water. Similar parameters of hematology, biochemistry, and serum proteins were monitored in all the animals and no deviations from normal values were observed. No evidence of toxicosis occurred in any of the sheep throughout the test period and weight changes were normal. Parturition was normal and no teratogenic effects were observed. No visible histopathological lesions attributable to methoprene were found in any of the sacrificed animals.

Subsequently, over 800 cattle have been given methoprene in the drinking water in a horn fly suppression test in Hawaii with no adverse effects to the animals after 3 months into the test (R. L. Harris, USDA, personal communication).

TH-6040 has been evaluated in our laboratory with chickens and the results have indicated an effect on fat deposition and growth when levels of 2.5, 25, and 250 ppm were present in the feed of 1-day-old chicks through 56 days. Male chickens averaged 3 lb, whereas hens were over 6 lb in body weight. Gross changes in organ weights were easily observed at all levels, and the secondary sex characteristics of the combs and waddles were underdeveloped in the roosters. Testosterone levels were sharply reduced in all treatment levels in the males. This study is yet incomplete in the consideration of all the parameters that we consider. Another test at lower levels will have to be done for determination of the no-effect level.

Siddall and Slade (*57*) showed that some selected acylic and aromatic JH had no acute oral toxicity. In mice, additional studies demonstrated JH analogs appeared to be completely nontoxic in preoral doses of 5-10 g/kg body weight in studies by Cruickshank (*58*) and Pallos et al. (*59*).

Siddall and Slade considered in their rat study most of the biochemical parameters that we did in our sheep, swine, and cattle studies and also found no significant differences between the treated animals and the untreated ones.

The criteria that were used for registration of an IGR (methoprene) for toxicological properties are shown in Table 1.

The environmental properties determined are shown in Table 2.

Table 1. Toxicological properties of methoprene.

Property	
Acute oral toxicity (rat)	> 34,600 mg/kg
Acute oral toxicity (dog)	LD_{50}=5000-10,000 mg/kg
Subacute oral studies (90 days, rat and dog)	No effects with 5000 ppm
Primary skin and eye irritation	Nonirritating
Acute dermal toxicity (rabbit)	Dermal LD_{50}=3000-10,000 mg/kg
Acute aerosol inhalation (rat)	No effects at 2000 ppm
Three-generation reproduction study (rat)	No effects at 2500 ppm
Teratology studies (rat, rabbit)	No effects at 1000 mg/kg
Dominant lethal mutagenicity	No effects at 2000 mg/kg
Static fish toxicity studies	
Bluegill	LD_{50} = 4.62 ppm
Channel catfish	LD_{50} > 100 ppm
Coho salmon	LD_{50} = 32 ppm
Trout	LD_{50} = 106 ppm
Crustacean toxicity studies	
Crayfish	LD_{50} = 100 ppm
Fresh water shrimp	LD_{50} = 100 ppm
White shrimp	LD_{50} = 100 ppm
Pink shrimp	LD_{50} = 100 ppm
Subacute oral feeding studies	
Mallard duck	LC_{50} > 10,000 ppm
Bobwhite quail	LC_{50} > 10,000 ppm
Chickens	LC_{50} > 4640 ppm
Reproduction studies (bobwhite quail and mallard duck)	No effects at 30 ppm
Mammalian hormone bioassay (mouse and rat)	No estrogenic, androgenic, anabolic or glucocorticoid activity

Table 2. Environmental properties of methoprene.

Property	
Persistence in soil (1 lb/acre)	Halflife < 10 days
Movement in soil	Remains in top few inches of soil
Persistence in water in field	Halflife < 2 days
Persistence in plants (1 lb/acre)	
Alfalfa	Halflife < 2 days
Rice	Halflife < 1 day
Uptake by plants	Wheat did not take up residues from treated soil
Fate in food chain	Does not accumulate in food chain
Fate in animals (mice, rats, guinea pigs, steers, or cows)	Rapidly metabolized and eliminated
Fate in fish (natural field conditions)	No accumulation
Effects on nontarget insects	No deleterious effects on nontarget species

With the present system of toxicological categories, the IGR would be in the generally regarded as safe (GRAS) category. Pesticides in categories other than safe are: highly toxic (parathion), moderately toxic (chlorpyrifos) and slightly toxic (malathion).

Because of these properties shown by the IGR, it is hard to visualize the occurrence of significant environmental problems, especially with the JHAs. In view of the rapid metabolism and degradation by both plants and animals, accrued harmful effects may be difficult to ascertain against species of wildlife. There exists no doubt that the materials would come into contact with nontarget species by external application or by ingestion. However, the usage of the materials would not be on a broad spectrum basis against several insects but would be directed toward individual species at a given time in the life cycle to obtain the best efficacy.

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